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1: J Am Soc Nephrol 2002 Feb;13(2):519-27

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Anti-CD28 Monoclonal Antibody Therapy Prevents Chronic Rejection of Renal Allografts in Rats.

Laskowski IA, Pratschke J, Wilhelm MJ, Dong VM, Beato F, Taal M, Gasser M, Hancock WW, Sayegh MH, Tilney NL.

Surgical Research Laboratory, Harvard Medical School Cambridge, Massachusetts.

ABSTRACT. The effects of a signaling anti-CD28 mAb (JJ319), which interferes with the CD28-B7 T cell costimulation pathway thought to be involved in the development of chronic rejection of organ transplants, was investigated. Functional, morphologic, and molecular changes in rat renal allografts were examined up to 24 wk after placement. Control Lewis rats, recipients of F344 kidneys, received a single dose of a nonspecific mouse mAb intravenously on the day of transplantation (group 1). Group 2 animals were given anti-CD28 mAb in similar fashion. Group 3 animals were treated with a short course of cyclosporin A (CsA), and group 4 received both anti-CD 28 mAb and CsA. The majority (>95%) of animals in groups 2, 3, and 4 survived throughout the follow-up, compared with 28% in group 1 ($P < 0.001$). Group 2 and 4 recipients produced negligible proteinuria, whereas group 1 controls developed progressively increasing proteinuria after 4 wk and group 3 animals developed proteinuria by 24 wk. Allografts in groups 2 and 4 were morphologically unremarkable at 24 wk. Kidneys of group 1 animals rapidly developed changes of acute rejection, and those that survived long-term showed extensive glomerulosclerosis and interstitial fibrosis. Changes of early chronic rejection were noted in group 3 grafts. By reverse transcriptase-PCR, expression of representative inflammatory factors interferon-gamma and interleukin-10 were significantly elevated at 24 wk only in the surviving group 1 animals. A single dose of a signaling anti-CD28 mAb administered at transplantation or in combination with a short course of CsA significantly prolonged recipient survival, normalized function, and preserved the morphology of renal allografts in an established model of chronic rejection. These data support an important role for T cell costimulation in the evolution of the chronic process.